Complete Summary

GUIDELINE TITLE

Management of infertility caused by ovulatory dysfunction.

BIBLIOGRAPHIC SOURCE(S)

American College of Obstetricians and Gynecologists (ACOG). Management of infertility caused by ovulatory dysfunction. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2002 Feb. 12 p. (ACOG practice bulletin; no. 34). [58 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Infertility due to ovulatory dysfunction caused by:

- Polycystic ovary syndrome (PCOS)
- Hypothalamic amenorrhea (hypogonadotropic hypogonadism)
- Hyperprolactinemia
- Premature ovarian failure (hypergonadotropic hypoestrogenic anovulation)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Diagnosis
Evaluation

Management
Treatment

CLINICAL SPECIALTY

Endocrinology
Obstetrics and Gynecology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To aid practitioners in making decisions about appropriate obstetric and gynecologic care
- To provide guidelines for management and treatment of ovulatory dysfunction that results in successful ovulatory stimulation and pregnancy

TARGET POPULATION

Women of reproductive age with ovulatory dysfunction seeking treatment for infertility

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Measurement of serum levels of follicle stimulating hormone (FSH), thyroid-stimulating hormone, and prolactin
2. Measurement of testosterone and dehydroepiandrosterone sulfate (DHEAS) in patients with evidence of hyperandrogenism
3. Ovulation documentation by basal body temperature evaluation or luteinizing hormone (LH) surge testing
4. Evaluation for male factor infertility by semen analysis
5. Hysterosalpingography if necessary

Management/Treatment

1. A Step-by-Step Approach to Ovulation Induction in Women with PCOS

   The least resource-intensive interventions are recommended in the early steps in the protocol, while the most resource-intensive interventions are reserved for later treatment.

   Step 1. If the body mass index (BMI) is higher than 30, recommend weight loss of at least 10% of body weight.

   Step 2. Prescribe clomiphene to induce ovulation.

Step 3. If DHEAS is higher than 2 mg/mL, consider combining clomiphene with a glucocorticoid to induce ovulation.

Step 4. If clomiphene does not result in ovulation, consider a combination of metformin plus clomiphene.

Step 5. Initiate low-dose FSH injections.

Step 6. Initiate low-dose FSH injections plus metformin.

Step 7. Consider laparoscopic ovarian surgery or in vitro fertilization.

2. Weight gain in women with hypothalamic amenorrhea and a BMI lower than 20

Note: Other treatments that were discussed but not recommended include human chorionic gonadotropin (HCG), ovarian diathermy, and dopamine agonists (bromocriptine, pergolide, cabergoline).

MAJOR OUTCOMES CONSIDERED

- Effect of weight loss on reproductive function
- Pregnancy rates associated with the use of clomiphene alone, clomiphene plus glucocorticoid, and clomiphene plus metformin
- Adverse effects of fertility drugs

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The MEDLINE database, the Cochrane Library, and American College of Obstetricians and Gynecologists' (ACOG's) own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and June 2001. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document.

Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial

II-1 Evidence obtained from well-designed controlled trials without randomization

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Analysis of available evidence was given priority in formulating recommendations. When reliable research was not available, expert opinions from obstetrician-gynecologists were used. See also the "Rating Scheme for the Strength of Recommendations" field regarding Grade C recommendations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A — Recommendations are based on good and consistent scientific evidence.

Level B — Recommendations are based on limited or inconsistent scientific evidence.

Level C — Recommendations are based primarily on consensus and expert opinion.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practice Bulletins are validated by two internal clinical review panels composed of practicing obstetrician-gynecologists, generalists and subspecialists. The final guidelines are also reviewed and approved by the American College of Obstetricians and Gynecologists (ACOG) Executive Board.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The grades of evidence (I-III) and levels of recommendations (A-C) are defined at the end of "Major Recommendations" field.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- In obese women with polycystic ovary syndrome (PCOS), weight loss should be considered because it is associated with a decrease in circulating testosterone concentration, an increase in the frequency of ovulation, and in some women, pregnancy.
- In obese women with PCOS who did not ovulate when treated with clomiphene, the combination of clomiphene plus metformin may be considered because the rate of ovulation is greater than it is with clomiphene alone.
- In women with PCOS and a serum dehydroepiandrosterone sulfate (DHEAS) level higher than 2 micrograms/mL, the combination of clomiphene plus glucocorticoid may be considered because the rate of ovulation is greater than it is with clomiphene alone.

- In women with hypothalamic amenorrhea and a body mass index (BMI) lower than 20, weight gain should be considered because it may be associated with the resumption of ovulation and pregnancy.
- In women with PCOS receiving gonadotropin injections for ovulation induction, low-dose follicle-stimulating hormone (FSH) may be considered because it is associated with a higher rate of cycles with the development of a single dominant follicle and fewer high-order multiple gestations.

Definitions:

Grades of Evidence

I Evidence obtained from at least one properly designed randomized controlled trial

II-1 Evidence obtained from well-designed controlled trials without randomization

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Levels of Recommendation

Level A — Recommendations are based on good and consistent scientific evidence.

Level B — Recommendations are based on limited or inconsistent scientific evidence.

Level C — Recommendations are based primarily on consensus and expert opinion.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Improved infertility treatment that results in successful ovulatory stimulation and pregnancy

POTENTIAL HARMS

Adverse Effects of Medications

Clomiphene citrate can be associated with luteal phase defects and the suboptimal production of cervical mucus.

The most common symptoms experienced by women taking clomiphene include vasomotor symptoms (20%), adnexal tenderness (5%), nausea (3%), headache (1%), and, rarely, blurring of vision or scotomata.

The main side effects associated with bromocriptine are nausea, vomiting, and orthostatic hypotension.

The most common side effects of metformin are gastrointestinal disturbances, including diarrhea, nausea, vomiting, and abdominal bloating. In rare cases, metformin therapy has caused fatal lactic acidosis. In most of these cases, renal insufficiency or severe hypoxia (congestive heart failure, septic shock) was present.

The use of induction agents such as clomiphene or gonadotropin injections is associated with increased risk of ovarian cancer in nulligravid women and women with a strong family history of ovarian cancer.

Injections with follicle stimulating hormone (FSH) and in vitro fertilization are associated with higher rates of multiple gestation.

Precaution

Metformin should be discontinued 48 hours before—and not restarted for 72 hours after—any radiologic test involving intravenous contrast or before surgery.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Contraindications to the use of clomiphene are pregnancy, hypersensitivity to the medication, and ovarian cysts.
- Women with liver dysfunction should not take metformin.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Feb

GUIDELINE DEVELOPER(S)

American College of Obstetricians and Gynecologists - Medical Specialty Society

SOURCE(S) OF FUNDING

American College of Obstetricians and Gynecologists (ACOG)

GUIDELINE COMMITTEE

American College of Obstetricians and Gynecologists (ACOG) Committee on Practice Bulletins-Obstetrics

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Not stated

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: None available

Print copies: Available for purchase from the American College of Obstetricians and Gynecologists (ACOG) Distribution Center, PO Box 4500, Kearneysville, WV 25430-4500; telephone, 800-762-2264, ext. 192; e-mail: sales@acog.org. The ACOG Bookstore is available online at the ACOG Web site.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on September 23, 2004. The information was verified by the guideline developer on December 9, 2004.

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